IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Marek Z. Kubin and Raymond G. Goodwin		
Serial No.:	09/667,859	Group No.:	1645
Filed:	09/20/2000	Examiner:	B. Li
Entitled:	**NK Cell Activation Inducing Ligand (NAIL) DNA and Polypeptides, and Uses Thereof**		

REQUEST FOR REHEARING PURSUANT TO 37 C.F.R. §41.52

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Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 41.52, Appellants request rehearing and reversal of the Board of Patent Appeals and Interferences' ("Board") May 31, 2007, Decision on Appeal ("Decision") in the above referenced matter for the following reasons, as explained in further detail below.

As to the obviousness holding:

1. Appellants are entitled to rehearing and reversal under 37 C.F.R. § 41.52(a)(2) because the Board's decision regarding the obviousness rejection is inconsistent with the Federal Circuit's June 28, 2007 decision in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd*,___F.3d _____, 83 U.S.P.Q.2D (BNA) 1169, 2007 WL 1839698(Fed. Cir. 2007) (copy attached as Appendix B for the Board's convenience). In *Takeda*, the Federal Circuit recently reaffirmed the correct analysis for obviousness of claims to chemical compounds in light of *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007), and reaffirmed *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995), in light of *KSR* in its affirmance of the non-obviousness of a chemical invention. The Board's characterization of *Deuel* here as discredited by the Supreme Court is,

therefore, contrary to the Federal Circuit's *Takeda* decision. The *Takeda* court also rejected *KSR*'s "obvious to try" test as inapplicable to the unpredictable chemical compound at issue in that case. The Board here extended *KSR*'s discussion of the "obvious to try" standard beyond its limits and contrary to the holding in *Takeda* by holding that the existence of an unisolated, uncoded protein, coupled with a general cloning methodology, somehow rendered obvious claims to polynucleotides encoding the hitherto unknown CD48 binding region of that protein.

2. In addition, pursuant to 37 C.F.R. § 41.52(a)(1), Appellants respectfully submit that the Board misapprehended or overlooked material facts that change the application of the law to the instant case:

(a) The Board overlooked or misapprehended the state of the prior art, and in particular Valiante *et al.* U.S. Patent No. 5,688,690 ("Valiante"). As an example, Valiante did not disclose or suggest that p38 would contain a CD48 binding region. To the contrary, Appellants were the first to discover that the claimed NAIL proteins contain a CD48 binding region, and were the first to identify that region. Indeed, the Board made no fact findings concerning knowledge in the art of the claim requirement for a CD48 binding region.

(b) The Board misapprehended Mathew *et al.*, 1993, J. Immunol. V. 151, 5328-5337 ("Mathew") by characterizing Mathew's cell surface signaling molecule, 2B4, as "the mouse version of Valiante's p38, the human version." Decision at 5, see also Decision at 10 ("Mathews exemplifies how the cDNA encoding 2B4, the mouse version of Valiante's p38 expressed on all NK cells, can be isolated and sequenced."). Mathew, however, does not disclose any relationship between 2B4 and p38. Indeed, the fact that 2B4 is the mouse version of Valiante's p38 was not in the prior art but instead is part of the teachings of Appellant's

specification. It is inappropriate to use Appellant's own application in support of the obviousness rejection.

(c) The Board incorrectly dismissed the compelling "teaching away" evidence of Mathew. Mathew teaches away from the claimed isolated polynucleotides because evidence that a gene is not transcribed, and therefore not expressed, indicates to one of ordinary skill in the art that expression cloning of such a gene using an antibody would be unsuccessful.

3. Conversely, if the Board did not rely upon Mathew's murine 2B4 molecule in support of the rejection, as it was by the Examiner below, then Appellants submit that the Board applied a new ground of rejection, based upon Valiante and Sambrook *et al.* Molecular Cloning: A Laboratory Manual, 2nd Ed. 2.43-2.84 (Cold Spring Harbor, N.Y. 1989) ("Sambrook") alone. Under 37 C.F.R. § 41.50(b), Appellants are entitled to an opportunity to respond to this new rejection.

4. Furthermore, the Board erroneously stated that Appellants did not separately argue the claims. Appellants expressly argued that claims 74-78 and 81-83 stand or fall separately from claim 73 (see Appeal Brief, pp 6, 7, and 18-22). The Board therefore failed to address the obviousness rejection of claims 74-78 and 81-83.

5. As to the written description rejection, the Board overlooked or misapprehended, and did not correctly consider, the state of the art when the invention was filed and whether one of skill in the art would recognize that the inventors had possession of the invention as claimed.

Accordingly, Appellants request that the Board (1) reconsider and now reverse its affirmance of the Examiner's obviousness rejection in light of the recent *Takeda* decision and the existing record; (2) acknowledge that its Decision has raised a new ground of rejection with respect to obviousness and provide Appellants an opportunity for response pursuant to 37 C.F.R.

§41.50(b); and (3) reconsider its affirmance and reverse the Examiner's written description rejection in light of the existing record.

I. The Claims Are Nonobvious

A. *In re Deuel* has not been overturned by *KSR*.

The Federal Circuit's recent decision in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, ___F.3d _____, 83 U.S.P.Q.2D (BNA) 1169, 2007 WL 1839698, confirms that *Deuel* is good law and highlights the error made by the Board in assessing obviousness. In *Takeda*, the Federal Circuit held that the "well-established" case law concerning *prima facie* obviousness of structurally similar compounds – the same law applied in *Deuel* – "is consistent with the legal principles enunciated in *KSR*." *Takeda* at *10. The Federal Circuit cited *Deuel* for the premise that a *prima facie* case of obviousness of a chemical compound is normally based on structural similarity. *Id.* As explained by the Federal Circuit, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to *modify a known compound* in a particular manner to establish *prima facie* obviousness of a new claimed compound." *Id*. (emphasis added). The *Takeda* court refused to find the invention obvious based upon *KSR*'s "obvious to try" discussion because the evidence showed that the claimed chemical compound was not obvious to try and that in fact the art taught away from the claimed compound.

Contrary to *Takeda*'s holding, the Board here did not compare the recited elements of the claims to any prior art structure or even combination of structures. Brushing aside *Deuel*, the Board stated that the

> Supreme Court recently cast doubt on the viability of *Deuel* to the extent the Federal Circuit rejected an "obvious to try" test. [citation omitted]. Under *KSR*, it's now apparent

> "obvious to try" may be an appropriate test in more situations than we previously contemplated."

Instead of adhering to *Deuel* and establishing a *prima facie* case of obviousness based on structural similarity of a known nucleic acid to the claimed nucleic acids, the Board erroneously applied an "obvious to try" test based on the availability of cloning procedures. Decision at 8-9.

Takeda stands in direct contrast to the Board's reasoning. There is no dispute that the claims in the instant application are to chemical compounds, in particular polynucleotides. Decision at 3 and 5. Yet the Board failed to properly establish a *prima facie* case of obviousness, since it cited no structurally similar prior art. For at least this reason, Appellants submit that the Board should reconsider its decision regarding obviousness.

B. A *Prima Facie* Case of Obviousness Has Not Been Presented

As enunciated in *KSR* and reaffirmed in *Takeda*, the *Graham* factors still control an obviousness inquiry. According to *Graham*:

> Under s 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966).

Applying these principles here, the facts, and in particular those overlooked by the Board, demonstrate that the claimed polynucleotides are non-obvious over the cited art.

1. The Scope and Content of the Prior Art, and the Level of Ordinary Skill in the Art

The Board correctly noted that Valiante disclosed the antibody C1.7 but did not provide any sequence information regarding p38. Decision at 4-5. However, Valiante only partially characterized the activities of the protein recognized by C1.7, noting that it appeared to be a 38 kD protein on a Western blot. The Board overlooked or misapprehended the fact that Valiante did not isolate the protein. This fact, as well as the fact that Valiante did not disclose any amino acid sequence, is contrary to the Board's finding that Valiante was "in possession" of p38's amino acid sequence. Decision at 6. Instead, Valiante disclosed a prophetic example for how one might use the antibody to clone the cDNA that encoded the protein that it recognized. This prophetic description, as well as the cited portions of Sambrook, were not the same methods Appellants used to clone human NAIL (see Specification at 65, Example 1, and discussion below in Section I. E.). Thus, there is no evidence to support the Findings of Fact No. 4 (Decision at 5) regarding the scope and content of Valiante and Sambrook. In addition, Valiante fails to teach or suggest that its p38 protein has a binding region for CD48, another point the Board overlooked or misapprehended.

Mathew discloses a murine 2B4 protein, as well as the cDNA that encodes that protein. But here, the Board ignored the significance of the fact that Mathew notes that a 2B4 homologue is not expressed in human NK cells. Mathew at 5333, col. 1. Contrary to the Board's argument, Mathew's disclosure was not interpreted by Mathew as merely conflicting data with respect to expression in humans, but as an indication of *no* expression in human NK cells.

Significantly, the Board also overlooked or misapprehended the fact that prior to Appellants' invention, the relationship between 2B4 and Valiante's p38 was unknown.

Appellants disclose in their specification that the murine 2B4 protein is the homologue of the human NAIL protein, but that fact was not known in the prior art. Specification at 13-16. Also unknown prior to Appellants' invention is the fact that CD48 is the counterstructure for human NAIL. *See*, for example, Specification at 66, and U.S. Provisional Application 60/096,750 at 64-65, filed August 17, 1998.

Finally, although the level of ordinary skill in the art is generally high, molecular biology was generally an unpredictable art at the time Appellants' application was filed. The Board acknowledged this fact in connection with its review of the enablement rejection, (Decision at 13), but failed to take it into account when assessing obviousness.

2. Differences Between the Prior Art and the Claims

The differences between the prior art and the claims are profound and can be illustrated by the following claim chart with reference to claim 73:

CLAIM 73	PRIOR ART
An isolated nucleic acid molecule comprising a polynucleotide	No nucleic acids encoding human NAIL had been isolated.
encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2,	The human NAIL protein had not been isolated, and no sequence information was known.
wherein the polypeptide binds CD48.	It was unknown that NAIL bound CD48 and, therefore it was unknown which portion of the NAIL protein bound CD48.

Before the claimed invention, no isolated polynucleotide sequence was known to encode any human NAIL protein. The human NAIL protein had not even been isolated, nor had any amino acid sequence information ever been obtained. It was also unknown that the function of the human NAIL protein was to bind to CD48.

The Board engaged in a hindsight analysis by positing that where the problem is to isolate NAIL cDNA, a person of skill in the art would be motivated to try methodologies available to clone the nucleic acid, thus making the claimed nucleic acid sequences obvious. *Id.* at 9. The Board relied on the following statement by the Supreme Court in *KSR*:

> Third, the court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

See Decision at 9, quoting *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 USPQ2d 1385, 1397 (2007).

KSR may suggest that, where a claim combines known elements to achieve a combination product exhibiting the expected functions of each element that it would have been "obvious to try," the combination could be obvious. However, there is no indication in *KSR* that obviousness could be based on the notion that it would be "obvious" to try a methodology for sequencing a gene from a protein disclosed in the prior art and then hope to arrive at the claimed structure with a binding site and properties attributable to that site completely unknown and unpredictable in the art. The Board's extension of *KSR's* reference to "obvious to try" to the facts and claimed invention in this case is unsupported and unjustified. In contrast to the context in which "obvious to try" is referred to in *KSR*, the claimed invention in the present case is not evident from any elements disclosed in the prior art or even from what the Board says is "obvious to

try." There is simply no prior disclosure of a CD48 binding region of p38, and no disclosure of any connection between p38 and 2B4. Applying "obvious to try" in this context improperly relies upon hindsight.

The Federal Circuit's decision in *Takeda,* which rejected obviousness based upon *KSR*'s "obvious to try" when the art is unpredictable, contradicts the Board's "obvious to try" test, which focuses only on the obviousness of trying a method of cloning. The Board's approach ignores the requirement, still in effect after *KSR*, that a *prima facie* case of obviousness for a new compound must be based on similarity of the new compound to a known compound. *Takeda* at *10. In addition, the Board's reliance on *KSR*'s reference to "a finite number, of identified, predictable solutions" is completely at odds with its express finding that the art is *unpredictable*. *Compare* Decision at 9 and 13. It is also at odds with the fact, overlooked by the Board, that the cited prior art failed to establish any connection between p38 and CD48. *See generally* Valiante and Mathew.

The Board's failure to determine the differences between the prior art and *what is claimed* is precisely the same failure the Federal Circuit was faced with in *Deuel*. The Federal Circuit, sitting *en banc*, held that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious …." *Deuel* at 1215. "Because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art." A *prima facie* case of obviousness in this situation, the Federal Circuit continued, must be based on *structural* similarity to a prior art compound. *Id.* at 1214. Since the claims at issue are directed to a new chemical entity in structural terms, *Deuel* and *Takeda* require that obviousness must be based on

structural similarity to a known compound. For these reasons, the Board has failed to provide reasons grounded in fact and law for holding that a *prima facie* case of obviousness has been established according to the well-established case law of the Federal Circuit.

C. The Dependent Claims 75-79 Are Also Non-obvious

The Board also asserted that Appellants did not separately argue the patentability of the dependent claims. This was in error.

Appellants grouped claims 73, 84, and 85, as standing and falling together. Appeal Brief at 6-7. Appellants noted that the remainder of the claims could not be grouped in view of each of the four issues on appeal (including obviousness), as described in detail below in Section VIII. Appeal Brief at 6-7. In section 8, Appellants specifically argued that the cited references failed to teach a single nucleic acid molecule within the scope of 73, 74, and 84-89, "much less the specific nucleic acid sequences specified in the remainder of the claims." Appeal Brief at 18. Appellants also noted the lack of any teaching in the cited reference of the specific sequences recited in claims 75-78 and 81-83. Appeal Brief at 20. Just as the broad claim 73 was not compared to any structure in the prior art, the prior art did not teach or suggest the specific structures recited in claims 75-78 and 81-83.

D. The Facts Overlooked or Misapprehended in the Decision Regarding The Mathew Reference Also Support Non-obviousness

The Board failed to grasp the significance of the fact that Mathew teaches away from the cloning of any human homologue of mouse 2B4. As established in the Appeal Brief, Mathew teaches that Northern blots conducted using human RNA indicate that a 2B4 homologue is not expressed in humans:

> Genomic Southern blots identified a human homologue of the 2B4 gene. However, RNA blot analysis of total RNA isolated from human NK cells suggests that 2B4 gene is not expressed in humans.

Mathew, p. 5330, column 1. The Board has not cited evidence to contradict the reported fact that 2B4 is not *expressed* in humans. Instead, the Board states that rather than teaching away, "this language merely indicates conflicting data existed regarding a 2B4 homolog in humans, with some data pointing to the existence of a human homolog." Decision at 10. But Mathew's indication of a human homologue does not conflict with its teaching that a human homologue of 2B4 is not expressed in human NK cells. Contrary to the Board's findings, therefore, Mathew would deter a person of skill in the art from trying to clone a human homologue of mouse 2B4 because if the gene is not expressed in humans, an antibody such as C1.7 could not be used to clone it. As in *Takeda*, when the prior art teaches one of ordinary skill away from the claimed invention, such a case "fails to present the type of situation contemplated by the [*KSR*] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.'" *Takeda* at *10.

The Supreme Court emphasized the importance of analyzing the interrelated teachings of the prior art when determining obviousness, and in particular in determining whether the prior art teaches away from the claimed invention. As noted by *KSR*, the Supreme Court in *United States v. Adams*, 383 U.S. 39 (1966), found an invention non-obvious by relying "upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be non-obvious." *KSR*, 127 S.Ct. at 1740. Here, the Board has incorrectly dismissed the fact that Mathew teaches away from the claimed invention, and thus failed to properly consider the interrelated teaching of the prior

art. When the teachings of Mathew are given proper weight, the claimed invention must be found to be non-obvious.

E. If The Obviousness Rejection Has Been Modified, Then it is a New Ground of Rejection Under 37 C.F.R. § 41.50(b)

Although the Board emphasized that the protein disclosed in Mathew is the murine homologue of the protein recognized by the C1.7 antibody of Valiante, the Board apparently did not combine Valiante and Sambrook with Mathew, as was asserted by the Examiner below. Instead, the Board found that Mathew is cumulative and merely exemplary. Decision at 8. It therefore appears that the rejection is now based merely upon the combination of Valiante and Sambrook. This is a new ground of rejection, for which Appellants have the right to present new arguments under 37 C.F.R. § 41.52(a)(3).

The Board assumed that, if the existence of a protein is known, and there is "a probe" to the protein available (in this case, an antibody) along with an alleged method for cloning, then the possession of that probe also confers possession of the polynucleotide encoding the protein. Specifically, the Decision states at 6:

> 14. Valiante's disclosure of the polypeptide p38, and a detailed method of isolating its DNA, including disclosure of a specific probe to do so, i.e., mAb C1.7, established Valiante's possession of p38's amino acid sequence and provided a reasonable expectation of success in obtaining a polynucleotide encoding p38, a polynucleotide within the scope of Appellant's claim 73. (*See* Valiante, col. 7, l.48 to col. 8, l. 7.)

As discussed above, this assumption is unwarranted in the field of molecular biology, an art which even the Board recognized was unpredictable. Decision at 13. Moreover, this conclusion is contradicted by *In re Wallach*, 378 F.3d 1330, a case upon which the Board relied.[1] Unlike the

[1] *Wallach* was cited for the proposition that "The state of the art had unquestionably advanced significantly during the ten year period between the time the *Deuel* application was filed in 1990 and Appellants' application was filed in

authors of the Valiante reference applied in this case, the appellants in *Wallach* had actually isolated a protein, TBP-II, and partially sequenced the amino terminus of the protein. *Wallach* at 1332. The claims at issue in *Wallach* related to polynucleotides encoding the functional TBP-II protein. The Federal Circuit soundly rejected the argument that possession of the isolated protein and knowledge of some of the amino acid sequence gave the appellants possession of the nucleotides encoding the functional protein. *Id* at 1334-1335.

Furthermore, contrary to the findings of fact nos. 4 and 9, the record is clear that the procedures outlined in Valiante and Sambrook are not the procedures that Appellants successfully used to isolate the gene encoding human NAIL. Instead, Appellants used a unique combination of conditions to generate their own natural killer cell cDNA libraries, and then applied various techniques (for example, a modification of the method of van der Merwe *et al.* involving Dynabeads® bead based separation) to finally identify a clone that encoded the human NAIL protein. See Specification at 65, Example 1. Given that even the authors of the Valiante reference, who had in hand the antibody C1.7 at least as early as 1993, never reported the cloning of p38 using the techniques prophetically described in Valiante or referenced in Sambrook, it cannot be concluded that such techniques would be successful.

II. The Written Description Rejection Fails to Consider the State of the Art

The Board held that the claims are not supported by an adequate written description. Decision at 17. The Federal Circuit's precedent clearly establishes that "[t]he applicant must . . .

2000." Decision at 6, citation omitted. As an initial matter, the priority date of Appellant's application is March 27, 1998. In addition, *Wallach* does not stand for this proposition. The complete quote from *Wallach* is "As a preliminary matter, we agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the 129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious." *Wallach*, 378 F.3d 1330, 1333.

convey to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). The Board never once addresses whether one of skill in the art would have recognized that the inventors were in possession of the claimed invention. This is particularly troubling in light of the following findings of fact by the Board:

> 24. The Specification "teaches in detail how to: 1) make variants of SEQ ID Nos: 1 and 2; 2) calculate the percent identity between SEQ ID Nos: 1 and 2 and the variant sequence; and 3) test the variant sequence to determine if it binds to CD48." (Br. 11; Reply Br. 6.)
>
> 27. At the time Appellant's application was filed, the level of skill in the relevant art (molecular biology) was high, as acknowledged by Appellants. (Br. 11.)
>
> 29. The "experimentation involved to produce other sequences within the scope of the claims" and thus to practice the full scope of claim 73, would have been "well within the skill of those in the art" (Br. 12) and thus would have been routine.

None of these facts are considered by the Board with respect to the written description analysis. Thus, the Board did not consider the skill in the art or the relevant state of the art at the time the application was filed. Nor did the Board consider that the Specification does describe specific amino acid changes that can be made and tested, such as, for example, conservative substitutions. Specification at 24-27. These omissions are in error in view of the Federal Circuit's recent decision in *Capon v. Eshhar* 418 F.3d 1349 (Fed. Cir. 2005); *see also Falkner v. Inglis*, 448 F.3d 1357; 79 U.S.P.Q.2D (BNA) 1001 (Fed. Cir. 2006). As held by the Federal Circuit "[t]he 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." *Capon* at 1357. The Federal Circuit gave the following specific guidance regarding written description:

> The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary with differences in the state of knowledge in the field and differences in the predictability of the science.

Id. The Board failed to consider any of these factors. Instead the Board erroneously states that: "Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement." Decision at 17. This finding is erroneous. The claims and specification provide both the structure of the claimed nucleic acid sequences and the function of the proteins encoded by the nucleic acids. Thus, there is a correlation between structure and function. The Board further admits those of skill in the art could have modified the disclosed nucleic acid sequences and screened them for the desired function. Decision at 13. Thus, in view of the state of relevant knowledge, those of skill in the art would have recognized the instant inventors had possession of the claimed invention.

Finally, Appellants respectfully request the Board reconsider its dismissal of the Office's *Synopsis of Guidelines for Written Description* as irrelevant in this case. The Federal Circuit relies upon the *Guidelines* as persuasive authority. *E.g., EnzoBiochem, Inc. v. Gen-Probe Inc.,* 323 F.3d 956 (Fed. Cir. 2002). Given the similarity of Example 14 of the *Guidelines* and the present case, Appellants submit that the *Guidelines* compel a finding that the written description requirement is met.

C. Conclusion

For the foregoing reasons, it is submitted that the Board's rejection of Claims 73 - 78 and 80 - 89 was erroneous. Appellants request that the Board (1) reconsider and now reverse its affirmance of the Examiner's obviousness rejection in light of the recent *Takeda* decision and the existing record; (2) acknowledge that its Decision has raised a new ground of rejection with respect to obviousness and provide Appellants an opportunity for response pursuant to 37 C.F.R. §41.50(b); and (3) reconsider its affirmance and reverse the Examiner's written description rejection in light of the existing record.

Dated: July 31, 2007

/J. Mitchell Jones/

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APPENDIX A

PENDING CLAIMS

The following is a list of the pending Claims.

73. An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

74. An isolated nucleic acid molecule of claim 73, wherein the polypeptide acid sequence is at least 90% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

75. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 22-221 of SEQ. ID NO:2.

76. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 1-221 of SEQ ID NO:2.

77. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-221 of SEQ ID NO:2.

78. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-224 of SEQ ID NO:2.

80. An isolated nucleic acid molecule comprising a polynucleotide at least 80% identical to SEQ ID NO:1.

81. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:6.

82. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:7.

83. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:8.

84. A recombinant vector comprising the nucleic acid molecule of any one of claims 73 through 83.

85. A host cell transfected or transduced with the vector of claim 84.

86. A method for the production of NK cell Activation Ligand (NAIL) polypeptide comprising culturing a host cell that has been genetically engineered to express the nucleic acid of claim 73 under conditions promoting expression of the polypeptide.

87. The method of claim 86, further comprising recovering the polypeptide.

88. The method of claim 87, wherein the host cell is a mammalian cell.

89. The method of claim 88, wherein the host cell is a CV-1/EBNA cell.

APPENDIX B

Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd,_ F.3d ___,

2007 WL 1839698 (Fed. Cir. 2007)

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Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.
C.A.Fed. (N.Y.),2007.
Only the Westlaw citation is currently available.
United States Court of Appeals,Federal Circuit.
TAKEDA CHEMICAL INDUSTRIES, LTD. and **Takeda** Pharmaceuticals North America, INC.,
Plaintiffs-Appellees,
v.
ALPHAPHARM PTY., LTD. and Genpharm, Inc.,
Defendants-Appellants.
No. 06-1329.

June 28, 2007.

Background: Owner of patent for diabetes drug brought infringement actions against proposed manufacturers of generic versions. The United States District Court for the Southern District of New York, Denise Cote, J., 417 F.Supp.2d 341, granted judgment for owner. Manufacturers appealed.

Holdings: The Court of Appeals, Lourie, Circuit Judge, held that:

(1) person of ordinary skill in the art would not have selected closest prior art compound as lead compound for antidiabetic treatment;

(2) person of ordinary skill in the art would not have been prompted to modify closest prior art compound, using steps of homologation or ring-walking, to synthesize claimed compound; and

(3) any error was harmless that district court may have committed by incorrectly implying that prosecution histories were not accessible to public.

Affirmed.

Dyk, Circuit Judge, filed concurring opinion.

[1] **Patents 291 ⚿16.25**

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases
Person of ordinary skill in the art would not have selected closest prior art compound as lead compound for antidiabetic treatment, and thus presumption of motivation did not apply on competitor's claim of obviousness; although prosecution history of patent included statement characterizing compound as "especially important," any suggestion to select compound was essentially negated given more exhaustive and reliable scientific analysis which taught away from compound and evidence from similar contemporaneously filed patents showed that there were many promising, broad avenues for further research. 35 U.S.C.A. § 103.

[2] **Patents 291 ⚿312(4)**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k312 Evidence
291k312(3) Weight and Sufficiency
291k312(4) k. Degree of Proof; Prima Facie Case. Most Cited Cases
Because a patent is presumed to be valid, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. 35 U.S.C.A. § 282.

[3] **Patents 291 ⚿324.5**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.5 k. Scope and Extent of Review in General. Most Cited Cases

Patents 291 ⚿324.55(4)

291 Patents
291XII Infringement
291XII(C) Suits in Equity

291k324 Appeal
291k324.55 Questions of Fact, Verdicts, and Findings
291k324.55(3) Issues of Validity
291k324.55(4) k. Novelty, Invention, Anticipation, and Obviousness. Most Cited Cases

Whether an invention would have been obvious is a question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial. 35 U.S.C.A. § 103.

[4] Patents 291 ⚿16(2)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(2) k. Prior Art in General. Most Cited Cases

Patents 291 ⚿16(3)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16 Invention and Obviousness in General
291k16(3) k. View of Person Skilled in Art. Most Cited Cases

Patents 291 ⚿36.1(1)

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k36 Weight and Sufficiency
291k36.1 Secondary Factors Affecting Invention or Obviousness
291k36.1(1) k. In General. Most Cited Cases

The factors that control an obviousness inquiry are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the pertinent art; and (4) objective evidence of nonobviousness. 35 U.S.C.A. § 103.

[5] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases

In a case involving a patent on a new chemical compound, some reason must be identified that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound. 35 U.S.C.A. § 103.

[6] Patents 291 ⚿16.25

291 Patents
291II Patentability
291II(A) Invention; Obviousness
291k16.25 k. Chemical Compounds. Most Cited Cases

Person of ordinary skill in the art would not have been prompted to modify closest prior art compound, using steps of homologation or ring-walking, to synthesize claimed compound in patent for antidiabetic treatment, and thus claimed compound was not obvious, where process of modifying lead compounds was not routine at time of invention, nothing in prior art provided reasonable expectation that adding methyl group to compound would have reduced or eliminated toxicity of lead compound, there was no reasonable expectation in the art that changing positions of substituent on pyridyl ring would have resulted in beneficial changes, and claimed compound differed significantly from lead compound, of which it was not a homolog, in terms of toxicity. 35 U.S.C.A. § 103.

[7] Patents 291 ⚿168(2.1)

291 Patents
291IX Construction and Operation of Letters Patent
291IX(B) Limitation of Claims
291k168 Proceedings in Patent Office in General
291k168(2) Rejection and Amendment of Claims
291k168(2.1) k. In General. Most

Cited Cases
Statement made during prosecution of patent for anti-diabetic treatment in response to enablement rejection, indicating only that changes to left moiety of lead compound would create compounds with same properties as compounds of prior art, did not represent that lower toxicity would result from change, for purpose of obviousness claim. 35 U.S.C.A. § 103.

[8] **Patents 291 ⚿324.56**

291 Patents
291XII Infringement
291XII(C) Suits in Equity
291k324 Appeal
291k324.56 k. Harmless Error. Most Cited Cases
Any error was harmless that district court may have committed by incorrectly implying that prosecution histories were not accessible to public, on competitor's claim of obviousness, where court nonetheless considered prosecution history of patent in its obviousness analysis and accorded proper weight to statements contained therein. 35 U.S.C.A. § 103.

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases

Patents 291 ⚿328(2)

291 Patents
291XIII Decisions on the Validity, Construction, and Infringement of Particular Patents
291k328 Patents Enumerated
291k328(2) k. Original Utility. Most Cited Cases
4,287,200. Cited as Prior Art.

4,340,605, 4,438,141, 4,444,779. Cited.

4,687,777. Valid.

Appealed from United States District Court for the Southern District of New York, Judge Denise Cote.

David G. Conlin, Edwards Angell Palmer & Dodge LLP, of Boston, MA, argued for plaintiffs-appellees. With him on the brief were Barbara L. Moore, Kathleen B. Carr, and Adam P. Samansky; and Anthony J. Viola and Andre K. Cizmarik, of New York, NY. Of counsel on the brief was Mark Chao, **Takeda** Pharmaceuticals North America, Inc., of Lincolnshire, IL.
Kevin F. Murphy, Frommer Lawrence & Haug LLP, of New York, NY, argued for defendants-appellants. With him on the brief were Edgar H. Haug and Jeffrey A. Hovden.

Before LOURIE, BRYSON, and DYK, Circuit Judges.
LOURIE, Circuit Judge.
Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively "Alphapharm") appeal from the decision of the United States District Court for the Southern District of New York, following a bench trial, that U.S. Patent 4,687,777 was not shown to be invalid under 35 U.S.C. § 103. ***Takeda*** *Chem. Indus., Ltd. v. Mylan Labs.*, 417 F.Supp.2d 341 (S.D.N.Y.2006). Because we conclude that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

BACKGROUND

Diabetes is a disease that is characterized by the body's inability to regulate blood sugar. It is generally caused by inadequate levels of insulin-a hormone produced in the pancreas. Insulin allows blood sugar or glucose, which is derived from food, to enter into the body's cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce

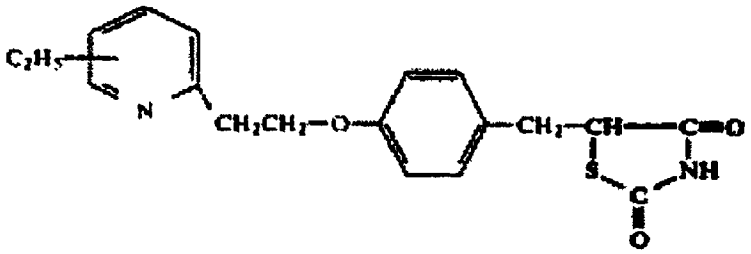
insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes-affecting over 90% of diabetic individuals.

In the 1990s, a class of drugs known as thiazolidinediones ("TZDs") was introduced on the market as a treatment for Type 2 diabetes. **Takeda** Chemical Industries, Ltd., and **Takeda** Pharmaceuticals North America, Inc. (collectively "**Takeda**") first invented certain TZDs in the 1970s. **Takeda's** research revealed that TZDs acted as insulin sensitizers, *i.e.,* compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the nucleus of the cell known as PPARgamma, which activates insulin receptors and stimulates the production of glucose transporters. *Takeda,* 417 F.Supp.2d at 348-49. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. *Id.*

Takeda developed the drug ACTOS®, which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS® has enjoyed substantial commercial success since its launch in 1999. By 2003, it held 47% of the TZD market, and gross sales for that year exceeded $1.7 billion. *Id.* at 386. The active ingredient in ACTOS® is the TZD compound pioglitazone, a compound claimed in the patent in suit.

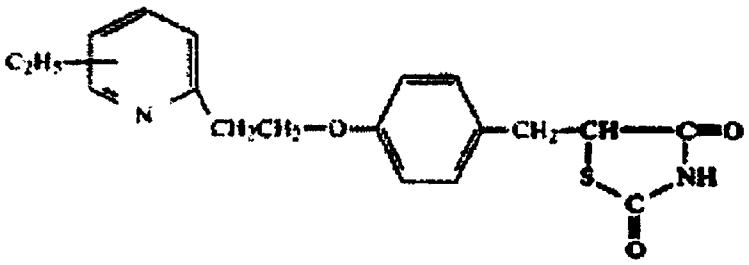
Takeda owns U.S. Patent 4,687,777 (the " 777 patent") entitled "Thiazolidinedione Derivatives, Useful As Antidiabetic Agents." The patent is directed to "compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." 777 patent col.1 ll.34-37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:



or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:

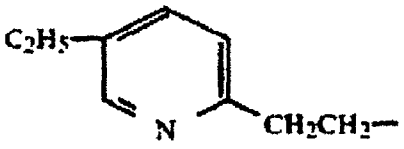


or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.
Id., claims 1 & 5.

For purposes of this appeal, the critical portion of the compound structure is the left moiety of the molecule, namely, the ethyl-substituted pyridyl ring. FN1 That chemical structure, which has an ethyl substituent (C^2 H^5) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, *viz.*, compounds with an ethyl substituent located at the four available positions on the pyridyl ring. *Takeda*, 417 F.Supp.2d at 360. The formula includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

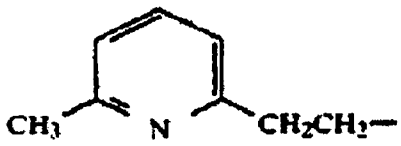
Claim 2 of the 777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:
2. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione.

777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:



Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. § 355(j) et seq. to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with its ANDA pursuant to § 505(j)(2)(B)(ii), asserting that the 777 patent is invalid as obvious under 35 U.S.C. § 103. In response, **Takeda** sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the 777 patent.

On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the 777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound that is referenced in Table 1 of the 777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH^3) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:



Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103. The court first concluded that there was no motivation in the prior art to select compound b as the lead compound for antidiabetic research, and that the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, **Takeda** would still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's nontoxicity. The court then rendered judgment in favor of **Takeda**. The district court also held that the 777 patent had not been procured though inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Standard of Review

[1][2][3] In this appeal, we are presented with one issue, namely, whether the asserted claims of the 777 patent would have been obvious under 35 U.S.C. § 103 at the time the invention was made. An invention is not patentable, *inter alia,* "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Because a patent is presumed to be valid, 35 U.S.C. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine,* 344 F.3d 1234, 1238-39 (Fed.Cir.2003). Whether an invention would have been obvious under 35 U.S.C. § 103 is a "question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.,* 464 F.3d 1286, 1289 (Fed.Cir.2006).

B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that such a conclusion is mandated by our case law, including our en banc decision in *In re Dillon,* 919 F.2d 688 (Fed.Cir.1990). Second, Alphapharm argues that the court erred in determining the scope and content of the prior art, in particular, whether to include the prosecution history of the prior 779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. **Takeda** contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. **Takeda** further argues that all of Alphapharm's remaining challenges to the district court's legal and factual rulings are simply without merit.

[4] We agree with **Takeda** that the district court did not err in concluding that the asserted claims of the 777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.,* --- U.S. ----, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR,* 127 S.Ct. at 1734 (quoting *Graham,* 383 U.S. at 17-18).

In a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four *Graham* factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

1. Differences Between the Prior Art and the Claims

a. Selection of Compound b as Lead Compound

Alphapharm's first argument challenges the court's

determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon*, 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed.Cir.1985).

We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.,* an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones*, 958 F.2d 347 (Fed.Cir.1992); *Dillon*, 919 F.2d 688; *Grabiak*, 769 F.2d 729; *In re Lalu*, 747 F.2d 703 (Fed.Cir.1984)).

[5] That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[FN2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

We agree with **Takeda** and the district court that Alphapharm failed to make that showing here. Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity.[FN3] Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, *i.e.,* replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered **Takeda's** U.S. Patent 4,287,200 (the " 200 patent"), which was issued on September 1, 1981, and its prosecution history. The court found that the 200 patent "discloses hundreds

of millions of TZD compounds." [FN4] *Takeda*, 417 F.Supp.2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection in order to show that the claimed compounds of the 200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the 200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. *Id.* at 375.

The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride lowering activity for 101 TZD compounds. Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered **Takeda's** 779 patent. That patent covers a subset of compounds originally included in the 200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." *Id.* at 353. The broadest claim of the 779 patent covers over one million compounds. *Id.* at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the 779 patent included the statement that characterized compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the 779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that **Takeda** filed contemporaneously with the 779 [p]atent showing that there were many promising, broad avenues for further research." *Id.* at 380.

The court found that the three compounds that the Sodha II reference identified as "most favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. *Id.* at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that there was nothing in the article that would recommend that a person of ordinary skill in the art choose

compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would "presumably not" be a suitable candidate compound for treatment of Type II diabetes. Alphapharm's expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find such side effects "undesirable."

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, **Takeda's** witness, Dr. Morton, testified that at the time Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm's assertion that *KSR,* as well as another case recently decided by this court, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed.Cir.2007), mandates reversal. Relying on *KSR,* Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within "the objective reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." Additionally, Alphapharm argues that our holding in *Pfizer,* where we found obvious certain claims covering a particular acid-addition salt, directly supports its position.

We disagree. The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Similarly, Alphapharm's reliance on *Pfizer* fares no better. In *Pfizer,* we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. *Pfizer*, 480 F.3d at 1363. Noting that our conclusion was based on the "particularized facts of this case," we found that the prior art provided "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." *Id.* at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that "did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects." Thus, *Pfizer* does not control this case.

Based on the record before us, we conclude that the district court's fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to prima facie obviousness of chemical compounds. Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as

the lead compound, and Alphapharm failed to prove that assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness. *See Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 (Fed.Cir.2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as a lead compound).

b. Choice of the Claimed Compounds

[6] Even if Alphapharm had established that preliminary finding, and we have concluded that it did not, the record demonstrates that Alphapharm's obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. *Takeda*, 417 F.Supp.2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were "routine steps in the drug optimization process," but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by **Takeda's** experts. *Id.* at 381. In addition, the court relied on Dr. Rosenberg's admission that a person of ordinary skill in the art would "look at a host of substituents, such as chlorides, halides and others, not just methyls" in modifying the pyridyl ring. *Id.*

Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that "homologation had no tendency to decrease unwanted side effects" and thus researchers would have been inclined "to focus research efforts elsewhere." *Id.* at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly from compound b in structure. *Id.* at 376 n. 51. Moreover, Dr. Mosberg agreed with **Takeda's** expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. *Id.* at 384-85. The court also found nothing in the 200 and 779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. Dr. Mosberg opined that the process of ring-walking was "known" to **Takeda**, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art that performing that chemical change would cause a compound to be more efficacious or less toxic. *Id.* at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl compounds.

Alphapharm relies on *In re Wilder*, 563 F.2d 457 (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In *Wilder,* our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to the human skin, whereas the isomer was toxic. The court held that "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." *Id.* at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homo-

log and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the homologue," and thus failed to rebut the presumption. *Wilder*, 563 F.2d at 460.

We would note that since our *Wilder* decision, we have cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," *Grabiak*, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of Wilder. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. *Takeda*, 417 F.Supp.2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of **Takeda's** Biology Research Lab and co-inventor of the 777 patent. That report contained results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone was "comparatively potent" and "showed no statistically significant toxicity." *Id.* at 356-57. During the following months, **Takeda** performed additional toxicity studies on fifty compounds that had been already synthesized and researched by **Takeda**, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. *Id.* at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, *Wilder* does not aid Alphapharm because, unlike the homolog and claimed compound in *Wilder* that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, **Takeda** rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

[7] Alphapharm also points to a statement **Takeda** made during the prosecution of the 779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the 779 patent, in response to an enablement rejection, **Takeda** stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That statement, however, indicates only that changes to the left moiety of a lead compound would create compounds with the same properties as the compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court correctly noted, the compounds disclosed in the 779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed *supra,* the district court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. We do not see any error in the district court's determination that one of ordinary skill in the

art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a prima facie case of obviousness because Alphapharm failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.[FN5]

2. Scope and Content of the Prior Art

[8] Alphapharm also assigns error to the district court's determination regarding the scope and content of the prior art. Alphapharm asserts that the court excluded the prosecution history of the 779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. **Takeda** responds that the court clearly considered the 779 patent prosecution history, which was admitted into evidence on the first day of testimony. **Takeda** urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the 779 patent and the file history that appears in the court's opinion.

We agree with **Takeda** that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecution history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. *Takeda*, 417 F.Supp.2d at 378. In considering the prosecution history of the 779 patent, the court noted that **Takeda** filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." *Id.* The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that **Takeda** was actively conducting research in many directions, and had not narrowed its focus to compound b." *Id.* at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, *see id.* at n. 59, *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955 (Fed.Cir.1986) ("[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered the prosecution history of the 779 patent in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the 777 patent have not been shown to have been obvious and hence invalid.

AFFIRMED

Concurring opinion filed by Circuit Judge DYK.DYK, Circuit Judge, concurring.

I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here-claim 2-is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of U.S. Patent No. 4,867,777 (" 777 patent")-which are also referenced in the judgment-renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5

were included in generic claims in the prior art U.S. Patent No. 4,287,200 (" 200 patent"). Unfortunately our law concerning when a species is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not necessarily render invalid a later claim to a species within that genus. *See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed.Cir.2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to claim a subset of that range. *See Application of Petering*, 49 C.C.P.A. 993, 301 F.2d 676, 683 (C.C.P.A.1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed.Cir.2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed.Cir.1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the 200 patent, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art 200 patent also generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the 777 patent, and admitted that there is no evidence of unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and 5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.

FN1. Pyridine is a "six-membered carbon-containing ring with one carbon replaced by a nitrogen." ***Takeda***, 417 F.Supp.2d at 351.

FN2. We note that the Supreme Court in its *KSR* opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. § 103 uses the language "would have been obvious," and the Supreme Court in *KSR* did consider the particular time at which obviousness is determined, we consider that the Court did not in *KSR* reject the standard statutory formulation of the inquiry whether the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. § 103. Hence, we will continue to use the statutory "would have been" language.

FN3. The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

FN4. Three divisional applications derive from the 200 patent. Those applications matured into U.S. Patent 4,340,605, U.S. Patent 4,438,141, and U.S. Patent No. 4,444,779 (the " 779 Patent"). The 779 patent is of particular relevance in this appeal and is discussed below. ***Takeda***, 417 F.Supp.2d at 378.

FN5. The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been shown to possess unexpected results sufficient to overcome a prima facie case of obviousness,

> and hence claims 1 and 5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

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